their attorneys. This is the 28 percent of the premium dollar. Assuming that awards do not decrease and that the one thousand Grange members have average performance and risk, the cost to the individual non-sued member would have been $850. This is a far cry from the premiums most of us pay at the present time.

Undoubtedly, there are many aspects of this Grange concept that need to be clarified and solved. But the legal framework *can* be developed. It is time that we explore *all* alternatives, and there is no reason that physicians themselves cannot develop a new system. Do we have to wait for someone else to do what we need done for ourselves? I would enjoy your comments and suggestions.

HARVEY E. KNOERNSCHILD, MD
*San Jose*

## Diabetic Microangiopathy

TO THE EDITOR: It has come to our attention that in a Medical Staff Conference on Diabetic Microangiopathy (West J Med 121:404-412, Nov 1974) Dr. Marvin Siperstein took rather questionable liberties with the statistics of data published by Dr. Paul Beisswenger and one of the undersigned (R.G.S.) on the composition of diabetic glomerular basement membrane.[1]

Dr. Siperstein claimed that the observation of a statistically significant elevation ($P<0.01$) of the hydroxylysine content of diabetic basement membranes depends entirely on the highest point in the group of eight diabetic cases and that omission of this point leads to a nonsignificant P value.

A careful statistical reanalysis of these data has indicated that Dr. Siperstein's contentions are unfounded and incorrect. The highest value of the diabetic cases does not meet the criteria for an "outlying observation"[2] and therefore can not be rejected. Indeed even when this highest number is excluded, a comparison of the normal and remaining diabetic cases still shows a significant difference ($P<0.02$). If Dr. Siperstein had been motivated to leave out the lowest rather than the highest diabetic point, which is equally unjustifiable, a P value of less than 0.005 between the two groups would have been obtained.

In a further attempt to detract from the data, Dr. Siperstein indicated that five of the eight diabetic cases are within normal limits ($\pm 2SD$). In fact this observation has no adverse implications since it only indicates that the groups overlap. Such overlapping frequently occurs between different groups, but it is the standard error of the mean which is utilized in determining whether or not the samples come from a single or two distinct populations.

In his presentation Dr. Siperstein fails to mention the additional compositional changes observed in the diabetic glomerular basement membrane[1] such as the decrease in lysine ($P<0.001$), increase in glucose ($P<0.01$) and increase in galactose ($P<0.001$).

The question of the relationship of control to the microvascular complications is one which is of great importance to practitioners and researchers in the field of diabetes. There is no general acceptance of Dr. Siperstein's statement that "It is now apparent to everyone who follows diabetic patients that these manifestations of diabetes progress rather inexorably, regardless of the degree of control." It is unfortunate that in his zeal to advance his point of view, Dr. Siperstein finds it necessary to distort not only this work of Beisswenger and Spiro but also the distinguished contributions of Williamson and of Bloodworth and Engerman.

ROBERT G. SPIRO, MD
*Professor of Biological Chemistry*

RAY E. GLEASON, PH D
*Principal Associate in Medicine (Mathematical Biology)*
*Harvard Medical School*
*Joslin Research Laboratory, Boston*
*Boston, Massachusetts*

**REFERENCES**

1. Beisswenger PJ, Spiro RG: Studies on human glomerular basement membrane—Composition, nature of the carbohydrate units and chemical changes in diabetes mellitus. Diabetes 22: 180-193, Mar 1973
2. Grubbs FE: Procedures for detecting outlying observations in samples. Technometrics 11:1-211, 1969

* * *

### The Author Replies

TO THE EDITOR: In my grand rounds of January 9, 1974 on diabetic microangiopathy [Medical Staff Conference. West J Med 121:401-412, Nov 1974], I discussed, and tried to put into perspective, the finding of an increase in hydroxylysine in diabetic basement membranes, which has been reported by Drs. Beisswenger and Spiro.[1,2] In their writings, Dr. Spiro and Dr. Beisswenger have emphasized that they have found "marked" and "consistent" increases in the *hydroxylysine* con-

tent of diabetic basement membranes.[3,4] These conclusions have understandably led to a widespread belief that such changes in basement membrane hydroxylysine levels may represent the biochemical basis for diabetic microangiopathy.

In my discussion of this finding, I first clearly stated that "there is indeed a statistically significant difference in the mean hydroxylysine values, of the eight diabetic and eight normal basement membranes." Regardless of the statistical significance of this difference, however, it is important from the standpoint of their physiologic significance to point out that the differences reported were neither so "marked" nor so "consistent" as these authors have stated in their publications. The difference in hydroxylysine content of the diabetic and normal groups averaged only 19 percent; and by omitting the one highest diabetic value two standard errors from each mean do overlap. Nonetheless, Dr. Spiro is absolutely correct in pointing out that this small difference in the means remains statistically significant ($P<0.02$) even when the highest diabetic point is omitted.

Secondly, however, I emphasized the inconsistency of the hydroxylysine data by pointing out that only three of the eight diabetic patients studied had basement membrane hydroxylysine values that were outside of the normal range. Quite aside from the difference between the means of the two groups, for a finding to be "consistent" in the eight diabetic patients that Drs. Spiro and Beisswenger studied it would seem apparent that more than *three* of the diabetic patients should show the lesion. If increased hydroxylysine were in fact responsible for the abnormalities in basement membrane that were present in the far advanced lesions examined, it is not unreasonable to ask why the majority, i.e., five of their eight diabetic patients, showed no significant change in basement membrane hydroxylysine content. Dr. Spiro's letter dismisses, but does not dispute this point.

Thirdly, as I also noted in my review, three other laboratories[5-7] have published data that refute the finding of an increase in hydroxylysine in diabetic renal basement membranes. Kefalides[7] concludes: "The results indicate that the slight increases in hydroxylysine and hexose content observed occasionally in diabetic GBM [glomerular basement membrane] preparations are of no statistical significance and cannot be attributed to increases in the activities of enzymes which hydroxylate lysine or glycosylate hydroxylysine, respectively." I believe, therefore, that one is quite justified in concluding, as I did, "that there is simply no solid evidence to indicate *consistent* biochemical change in the primary structure of the basement membrane of the diabetic kidney."

Finally, regarding the inexorable progression of diabetic retinopathy, the point made was simply that the best control does not prevent retinopathy. Whether the rate of progression of the lesion can be influenced by better or poorer control was explicitly and purposely not discussed in this Medical Staff Conference. The point that retinopathy cannot be *prevented* in the vast majority of the diabetics is probably best documented from the data published from Dr. Spiro's institution, which has reported that 90 percent of diabetic patients manifest diabetic retinopathy after the third decade of their disease.[8] In this regard, Oakley et al have recently reported that those few diabetics who do escape retinopathy after 40 years of diabetes had been no better controlled than those who do develop retinopathy.[9] While no one advocates poor control of the diabetic, in view of these data, I doubt whether many clinicians today really believe that the best control that we are capable of delivering to our diabetics really prevents, or even arrests, diabetic retinopathy.

MARVIN D. SIPERSTEIN, MD, PH D
*Professor of Medicine*
*Chief, Metabolism Section*
*University of California Service*
*Veterans Administration Hospital, San Francisco*

**REFERENCES**

1. Beisswenger PJ, Spiro RG: Human glomerular basement membrane—Chemical alteration in diabetes mellitus. Science 168: 596-598, May 1, 1970

2. Beisswenger PJ, Spiro RG: Studies on the human glomerular basement membrane—Composition, nature of the carbohydrate units and chemical changes in diabetes mellitus. Diabetes 22: 180-193, Mar 1973

3. Spiro RG: Biochemistry of the renal glomerular basement membrane and its alterations in diabetes mellitus. N Engl J Med 288:1337-1342, Jun 1973

4. Beisswenger PJ: Specificity of the clinical alteration in the diabetic glomerular basement membrane. Diabetes 22:744-750, Oct 1973

5. Lazarow A, Speidel E: The chemical composition of the glomerular basement membrane and its relationship to the production of diabetic complications, *In* Siperstein MD, Colwell AR Sr, Meyer K (Eds): Small Blood Vessel Involvement in Diabetes Mellitus. Washington, D.C., American Institute of Biological Sciences, 1964, p 127

6. Westberg NG, Michael AF: Human glomerular basement membranes—Chemical composition in diabetes mellitus. Acta Med Scand 193:39-47, Jul-Aug 1973

7. Kefalides NA: Biochemical properties of human glomerular basement membrane in normal and diabetic kidneys. J Clin Invest 53:403, 1974

8. White P: Childhood diabetes—Its course, and influence on the second and third generations. Diabetes 9:345, 1960

9. Oakley WG, Pyke DA, Tattersall RB, et al: Long-term diabetes—A clinical study of 92 patients after 40 years. Q J Med New Series, 43:145-156, Jan 1974